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Ormeloxifene - A Newer Drug in The Management of Dub

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INTRODUCTION-

Menstrual disorders are one of the most common gynaecological condition resulting in hospital referrals. Approximataly , 20 to 30 % of women , in the age group of 35 to 50 years , seek to medical help for heavy menstrual bleeding . Today the total span of menstruating years has increased due to early menarche and late menopause and women are increasingly unwilling to accept menstrual problems as they represent a major sector of paid force in both the developing as well as developed countries. Surgical therapy appears more promising . Though the option is relatively safe with low mortality , one cannot deny the morbidity associated with hysterectomy. In the recent years, concern has been expressed about possible long term complication of hysterectomy like premature ovarian failure, cardiovascular disease and intestinal or urinary dysfunction. Thus more and more women are looking forward to an effective medical therapy. Ormeloxifene is one of the selective oestrogen receptor modulators[1]or SERMs, a class of medications which acts on the oestrogen receptor. In some parts of the body ,its action is oestrogenic (e.g.in the bones),in other parts of the body, its action is anti-oestrogenic (e.g.in the uterus and the breasts). It is best known as a non hormonal , non steroidal oral contraceptive which is taken once per week. In India, ormeloxifene has been available as a birth control product since the early 1990s, and it is currently marketed here under the brand name of, SAHELI [1]. Ormeloxifene has also been licensed under the trade names of, NOVEX-DS, CENTRON and Sevista. Ormeloxifene is primarily used as a contraceptive,but it may also be effective for dysfunctional uterine bleeding and advanced breast cancer. Ormeloxifene has also been tested in experimental settings as a treatment for menorrhagia. Its use in the treatment of mastalgia and fibroadenoma has also been discribed . It causes an asynchrony in the menstrual cycle between the ovulation and the development of the uterine lining ,although its exact mode of action has not been well defined.The effect of this SERM on the vascular endothelium leads to decrease in the blood loss and there by amelioration of symptoms in dysfunctional uterine bleeding (DUB). With this background the present study was undertaken to study the efficacy of ormeloxifene in the treatment of AUB and effect of drug on the endometrium and side effects , besides patients acceptability and compliance.

MATERIALS AND METHODS

This prospective analytical study was carried out at tertiary care hospital attached with Govt. medical college Kota over a period of one year. 50 patients with DUB over the age of 35 years were included in the present study .Those with history of abortion within 3 months or childbirth within one year or those desirous of childbearing were excluded. Likewise IUCD or pill users or those with autoimmune diseases, diabetes, thyroid , liver or coagulation disorders or those with congenital anomaly of uterus were also excluded.

The main presenting complaints were bleeding PV, pain in the abdomen, a white discharge and irregular menstrual cycles. The mean age of the study group was 40 +- 5 years . An institutional ethical clearence for the study was taken. An informed consent was obtained from the patients who were selected for the study . The subjects were selected randomly. All the patients were admitted and the causes for the abnormal uterine bleeding were rule out by taking the history, by doing a clinical examination and by doing investigations like complete blood count , coagulation profile , thyroid profile, ultrasonogram of the abdomen and pelvis and dilation and curettage. After ruling out the possible causes of the abnormal uterine bleeding , a diagnosis of DUB was made and the treatment with ormeloxifene was started . The treatment with ormeloxifene was evaluated by measuring the PBAC -score, Hb g/dl and the endometrial thickness before and after 6 months of treatment with ormeloxifene. Ormeloxifene was given in the doses of 60 mg tablet twice a week for 3 months , followed by once a week for another 3 months .

Endometrial thickness using trans vaginal sonography (TVS) was carried out pretreatment and after 6 months of treatment to study the response of the endometrium to the drug. The side effects and relief of symptoms and patient acceptability were studied. All the patients were followed up till 6 months of the treatment.

Pictorial blood assesment chart (PBAC) was used to measure the menstrual blood loss (MBL) .The women were asked to used certain sanitary napkins which have similar absorbant capacities. They recorded the number of sanitary napkins used each day and the degree of soiling of each pad used. Number and sizes of clots passed were also noted. Scores were assigned to different degrees of soiling of sanitary napkins and number and sizes of clots passed. A PBAC score of greater than or equal to 100 was considered diagnostic of menorrhagia. MBL, passage of clots, blood haemoglobin levels and ET in proliferative phase by TVS were the main outcome studied.

RESULTS

Around 70 women with menorrhagia were screened , 50 were found eligible and consented to participate . All of them completed the 6 months follow up and were included in the analysis.

Clinical characteristics of the patients are shown in Table 1. Median age of the patients was 40 years with a range of 35 -45 . Most of the patients were multipara with a median parity of 3 . Duration of symptoms was quite long with a mean duration of 1.8years before starting the therapy. Severity of disease was estimated by the median number of sanitary napkins used per cycle, which was 16 . Most of the patients were anaemic with a mean Hb of 8.6gm% at the time of presentation.

Mean PBAC score before treatment was 375 and the mean PBAC score after 1 month of treatment with ormeloxifene was 206.25.i.e. it had reduced by 45%. At the end of the third month PBAC score had reduced by 84.6% from the baseline. There was a significant reduction(p= 0.014).The mean PBAC score at the end of the study period was 47 (Table-2) , reporting an overall reduction in the mean blood loss by 87.5%. Thus there was a significant reduction (P value <0.001) in mean blood loss in patients recieved ormeloxifene.

The details of Hb gm/dl are given in [Table-3].Most of the patients were anaemic at the start of the study with a mean Hb of 8.6 gm/dl. There was a significant improvement in the Hb level (P value <0.001) after 6 months of treatment with ormeloxifene. As shown in the table, mean Hb after therapy was 11.5gm/dl.

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The P values which were obtained by using the Student t test(Paired),were presented in Mean +-SD.

The mean endometrial thickness before treatment was 8.36mm. The mean endometrial thickness after treatment with ormeloxifene was found to be 4.89mm (Table-4). There was a significant reduction in the endometrial thickness in patients recieved ormeloxifene (P value <0.001).

The predominent side effect noted with ormeloxifene was amenorrhea and was found in 12% of women.(Table-5)

DISCUSSION

DUB is a diagnosis of exclusion, other conditions like uterine fibroids, endometrial polyps and systemic diseases must be excluded by appropriate investigations . The exact mechanism is uncertain but is believed to be caused by dysfunction of hypothalamic- pituitary- ovarian axis (2). The current medical options include high dose estrogens, combined estrogen and progesterones or progesterone alone, gonadotropin releasing hormone agonists, nonsteroidal anti-inflammatory drugs, danazol and antifibrinolytics.

The approach to the management is to ensure general wellbeing and to improve quality of life in addition to control of bleeding .Medical management and avoidance of surgery is always recommended, as the short period of drug therapy bridges the temporary phase of menstrual alterations successfully, where in young subjects settle down with normal cycles and elderly with menopause (2).

Preference should be for non steroidal agents as steroidal agents will only aggravate the existing endocrine dysfunction. Ormeloxifene, a non steroidal drug, is easier to administer, cost effective, and has lesser side effects(3,4).

The mean PBAC score at the end of the study was 47. The overall reduction in mean blood loss was 87.5%.A study conducted in 2000 on 70 subjects using ormeloxifene in a dosage of 30mg twice weekly for 6 months reported a reduction in menorrhagia by 80 to 87.78%(5).A similar study was conducted on 42 women with menorrhagia administering ormeloxifene 60 mg twice weekly for one month showed reduction in menorrhagia by 99.7% at 4 months (6).The result of the present study were comperable with the result of the other study.

Reduction of the endometrial thickness is definitely objective evidence showing reduction in mean blood loss. In the present study , there was a significant reduction the endometrial thickness. A similar study using ormeloxifene in DUB showed significant reduction in ET after 6 months of treatment(7). It was observed that 80 % of the subjects, who failed to respond to ormeloxifene, had ET < 5mm.

Although a number of drugs are available, there is a general lack of an evidence based approach, marked variation in practice and continuing uncertainty regarding the most appropriate therapy . Cyclical combined oral contraceptive pills were widely used previously but the side effects have limited their use in DUB. Danazol , gestrinone and gonadotropin-releasing hormone analogs are all effective in terms of reducing menstrual blood loss but adverse effects and cost limit their long term use(4).

The ideal therapy should be a designer drug , which can block the action of estrogen on the endometrium but not its beneficial effects on other tissues. SERMs, by virtue of their tissue selective pharmacology have attracted attention of researchers in recent years. SERMs have effects on tissues containing estrogen receptors, such as bones, breast, uterine and genitourinary tissues, brain and on markers of cardiovascular risk. Current evidence indicates that each SERM has a unique array of clinical activities (4).

Ormeloxifene is one such multifunctional nonsteroidal SERM possessing potent estrogen antagonistic activities and has been marketed in india as once a week oral oral contraceptive. It causes no uterine stimulation , prevents bone loss , has no risk of breast cancer , a positive effects on lipids and cardiovascular system and maintains cognitive functions of brain. It is indicated for the treatment of DUB at any age. It offers additional advantage of relief of premenstrual syndrome in perimenopausal women. In a pilot study , ormeloxifene was found as a effective and safe therapeutic option for the medical management of menorrhagia (6).

Although, the assessment of menstrual flow is highly subjective and gauging the severity of the condition by objective assessment of menstrual blood loss is difficult, PBAC score is widely used to estimate MBL. In addition to PBAC, we have also assessed the number of sanitary napkins used per cycle and change in Hb levels of the patients. After six months of ormeloxifene therapy , there was a significant reduction in mean PBAC score , the number of sanitary napkins used , and duration of days of menstruation .There was a rise in Hb level of the patients.

Ormeloxifene was very well tolerated and practically there were no undesirable side effects. Amenorrhoea has been reported as a side effects with this drug in as high as 43%of the recepients (6). However , we encountered this adverse effect in only 12% 0f the patients. Other side effects of of ormeloxifene includes, nausea , vomiting headache , gastric dyspepsia, cervical erosion and discharge, ovarian cysts . Delayed menstrual cycle has been reported in some series,but if the tablet is taken regularly, it is of no concern.

Ormeloxifene has an excellent therapeutic index and is considered safe for chronic administration (6). However, there exists few contraindication like history of jaundice of liver dysfunction, pcos,cervical dysplasia, chronic cervicitis ,history of hypersensitivity to the drug, nursing mothers, chronic illness , renal disease and tuberculosis.

Table 1. Clinical characteristics of patients

Age in years	40+-5
Parity	3+_2
Duration of symptoms in years	1.8+-0.8years
Number of days of menstruation	9+_2
No. of sanitary napkins used per cycle	16+-2

Table 2. PBAC score before and after treatment

PBAC Score	Before treatment	After treatment
<100	-	43
100-300	32	7
>300	18	-
Mean	345	47
P value		<0.001

Table 3. Hb g/dl before and after treatment

Hb g/dl	Before treatment	After treatment
<7g/dl	7	-
7-9g/dl	22	7
9-11g/dl	17	29
>11g/dl	4	14
Mean Hb	8.6	11.5
P value		<0.001

Table 4. Endometrial thickness before and after treatment

Endometrial thickness	Before treatment	After treatment
0-5mm	6	26
5-10mm	25	13
10-15mm	19	1
Mean	8.36+-2.36	4.89+-1.60
P value		<0.001

Table 5. Side effects of ormeloxifene

Side effect	No.of cases (%)
Amenorrhoea	6 (12.0%)
Hypomenorrhoea	4 (8.0%)
Spotting	0
Pain abdomen	4(8.0%)

CONCLUSION

Ormeloxifene significantly reduces blood loss in patients of AUB as evidenced by decrease of PBAC score, reduction in number of sanitary napkins used, reduction in duration of menstruation and rise in haemoglobin levels. Amenorrhoea and hypomenorrhea with the use of ormeloxifene were a desirable side effects in the perimenopausal age group in which they were detected. The ease of administration of the drug facilitates patient compliance and acceptability and the marked relief of symptoms results in higher clientele satisfaction. Ormeloxifene should be the drug of choice in AUB patients after childbearing but used with caution and after counselling in the perimenopausal age group.

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